REMARKS

Claims 1-22 and 66-85 are pending in this application. Claims 2, 6, 14, 17 and 23-65 have been cancelled. Claims 1, 3-5, 7-13, 15, 16, 18, 19 and 22 have been amended and support for these amendments can be found in the specification, e.g., at page 3, line 16 to page 7, line 26, and page 31, lines 6-23. New claims 66-85 have been added. The new claims and amendments add no new matter.

Election/Restrictions

Applicants wish to thank the Examiner for extending the courtesy of discussing this application with applicants' undersigned representative Laurie Butler Lawrence on April 12, 2006. Applicants acknowledge that the Examiner has rejoined restriction groups I, II and III.

Rejections Under 35 U.S.C. § 112, second paragraph (Indefiniteness)

Claims 2, 6, 9, 11, 13 and 22 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

According to the Office Action, "[c]laims 9, 11, and 22...are indefinite for reciting 'portion of the heavy chain' because the exact meaning of the phrase is not clear. Is the 'portion' the variable region of the heavy chain or is it a portion of the variable region itself?"

Independent claims 9 and 11 are drawn to nucleic acid molecules that include a nucleotide sequence encoding a humanized immunoglobulin light or heavy chain (or antigen-binding fragments thereof), respectively. The claims have been amended to recite that the light or heavy chains (or antigen-binding fragments thereof) have an amino acid sequence comprising at least an antigen binding portion of the light or heavy chain variable region of specific amino acid sequences. It is clear from the language of the claims that the encoded light or heavy chain includes at least an antigen binding portion of the light chain or heavy chain variable region. It would be clear to one of ordinary skill in the art that antigen binding portions include the CDR regions contained in either the light or heavy chain variable region such that when paired with

the complementary region of the corresponding heavy or light chain, the immunoglobulin molecule has the ability to bind to a mammalian CCR2 polypeptide.

Independent claim 22 is drawn to a fused gene encoding a humanized immunoglobulin light chain. The light chain includes three CDRs from monoclonal antibody 1D9 and a framework region from HF21/28 antibody, and a second nucleic acid sequence encoding at least a portion of a constant region of an immunoglobulin of human origin. Applicants respectfully submit that the meaning of "a portion of the constant region of an immunoglobulin of human origin" is entirely clear from the claim language and the specification. For example, the portion can be a portion of the κ and λ (light chain) or a portion of a γ, μ, α, δ or ε (heavy chain) of a human immunoglobulin. See, for example, page 32, lines 9-18 of the instant application.

Claims 2, 6, 13, and 22 are also rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

According to the Office Action, "[c]laims 2, 6, 13, and 22 are indefinite for reciting the term 'derived'. The term 'derived' is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification."

Applicants respectfully disagree with this characterization and submit that it is entirely clear from the specification what "derived from a human framework region" refers to (see, for example, page 32, line19, to page 34, line 3, of the instant specification). However, solely in order to expedite the prosecution of this application, Applicants have herein amended claims 2, 6, 13, and 22 by removing the word "derived." As amended, the claims recite that the framework region is from HF 21/28 antibody with regard to the light chain and from 4B4 'CL antibody with regard to the heavy chain. Based upon the knowledge in the art and the teachings provided in the instant application, it would be clear to a person of ordinary skill in the art that a framework region from either HF 21/28 antibody or 4B4 'CL antibody indicates that the framework region is a human sequence from HF 21/28 antibody or 4B4 'CL antibody that has been modified to make it humanized. In view of these amendments, the rejection of these claims is rendered moot.

Applicants also note that the claim language regarding the encoded light chain or heavy chain is open ended. Therefore, the sequences can further include, for example, a detectable marker.

For the reasons provided above, Applicants respectfully request that the Examiner withdraw this rejection.

Rejections Under 35 U.S.C. § 112, first paragraph (Enablement)

At pages 4-6, the Office Action indicates that a deposit under the Budapest Treaty, must be made for the 1D9 monoclonal antibody. The hybridoma cell line producing the antibody according to the present invention was deposited on July 17, 1998, on behalf of LeukoSite, Inc., 215 First Street, Cambridge, Mass. 02142, U.S.A. (now Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge, MA 02139, U.S.A.), at the American Type Culture Collection, 10801 University Boulevard, Manassas, Va. 20110, U.S.A., under Accession No. HB-12549 (1D9). Applicants also submit herewith a Declaration of Availability for this hybridoma.

The Office Action also indicates that a deposit under the Budapest Treaty, is suggested for the HF-21/28 and 4B4'CL antibodies. Specifically, the Office Action states that the claims "recite the light chain of the human HF21/28 antibody and the heavy chain of the 4B4'CL antibody and as such encompass not only the variable heavy chain but the constant heavy chain and as such the entire sequence is not disclosed in this application."

Applicants respectfully traverse this rejection. The claims actually recite "a framework region" of either the 4B4'CL antibody or HF21/28 antibody and Applicants respectfully submit that the framework sequences of both of these antibodies are disclosed in the present application and in the incorporated references Chastagner et al. (1991) Gene 101(2):305-6 and Sanz et al. (1989) Journal of Immunology 142:883. Furthermore, the framework sequence of the HF 21/28 and 4B4'CL antibodies are available at the Kabat Database under database Nos: 005056 and 000490, respectively. Thus, based on the knowledge in art and the guidance provided in the application, a skilled artisan could make and use the claimed nucleic acids without undue experimentation.

Rejections Under 35 U.S.C. § 112, first paragraph (Written Description)

(2) At pages 6-8 of the Office Action, claims 2 and 10-14 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description.

According to the Office Action, "[t]he instant specification provides insufficient description of the claimed genus of all antibodies having binding specificity for CCR2 and a genus of any framework region derived from a light and heavy chain of human origin."

Furthermore, the Office Action cites case law to allege that,

> the skilled artisan cannot envision the detailed structure of the encompassed genus of genes encoding all CDRs having binding specificity for CCR2 and genes encoding all framework regions of human origin, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Applicants respectfully traverse this rejection and provide the following remarks to show that the specification does provide adequate written description for claims 2 and 10-14.

First, Applicants note that claims 10-12 specifically recite either a specific amino acid sequence encoded by the nucleic acid or a specific sequence of the nucleic acid. Since these claims recite the sequence, it is clear that a skilled artisan could envision the structure of the claimed nucleic acid molecules.

Claim 14 has been cancelled thereby obviating the rejection with respect to claim 14. Claim 2 has also been cancelled but the limitation of claim 2 is now in claim 1. Thus, Applicants address this rejection below.

The Office Action incorrectly characterizes the claims as covering "all CDRs having binding specificity for CCR2". The claims do not recite any CDR having binding specificity to CCR2. Instead, the claims recite that the CDRs are from murine 1D9 antibody. As the entire sequence of murine 1D9 monoclonal antibody including the sequence of the CDRs are disclosed in the present application (see, e.g., Figures 7 and 8), a person of ordinary skill in the art could

readily envision the structure of antibodies or antigen binding fragments thereof that include these CDRs.

With regards to the statement in the Office Action that "a skilled artisan cannot envision ... genes encoding all framework regions of human origin", Applicants note that claim 1 recites that the framework region is from HF 21/28 antibody and not any human framework region as alleged in the Office Action. The framework regions of HF 21/28 antibody are disclosed in the present application (see, for example, Figure 11) and were known in the art at the time of filing. Moreover, based on the knowledge in the art at the time of filing and the disclosure of the instant application, a skilled artisan could envision modifications that can be made within the framework region of HF 21/28 antibody to provide a humanized immunoglobulin light chain. For example, page 93, line 15 through page 94, line 15 provides guidance as to which amino acids within the framework regions of HF 21/28 antibody should be conserved. Applicants also describe framework regions of five different humanized light chains from HF 21/28 antibody. Thus, in view of the knowledge in the art, a skilled artisan upon reading the specification would have been readily able to envision the claimed nucleic acids and thus would have thought the Applicants were in possession of the claimed invention at the time of filing.

For the reasons discussed above, Applicants respectfully request that the Examiner withdraw this rejection.

Rejections Under 35 U.S.C. § 112, first paragraph (Enablement)

(1) At pages 8-10, claims 13-15 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Applicants respectfully traverse this rejection.

According to the Office Action,

> the specification...does not reasonably provide enablement for any nucleotide sequence encoding a CDR of a light and heavy chain that have binding specificity to CCR2...[and] does not reasonably provide enablement for any framework region derived from a light and heavy chain of human origin.

....

The person of ordinary skill in the art would require to do an undue experimentation to practice the invention as claimed. (Office Action, page 8, lines 6-17.)

Applicants respectfully disagree with respect to the claims as amended and provide the following remarks, which show that the specification does provide enablement for (i) a genus of nucleotide sequences encoding CDR1, CDR2, and CDR3 of monoclonal antibody 1D9 and (ii) a genus of framework regions from the light chain of HF 21/28 antibody.

Claim 13 is drawn to an expression vector that includes a nucleotide sequence encoding CDR1, CDR2, and CDR3 of monoclonal antibody 1D9 and a framework region from a light chain of antibody HF 21/28. Claim 14 has been cancelled and claim 15 is a cell that includes the vector of claim 13.

The instant application provides sufficient description of CDRs 1-3 of monoclonal antibody 1D9 and of framework regions from the light chain of HF 21/28 antibody to make and use the claimed nucleic acids encoding such regions. For example, Figure 7 of the application provides the amino acid sequence of the CDRs of monoclonal antibody 1D9. In addition, an example of a nucleic acid sequence encoding the CDRs of monoclonal antibody 1D9 are provided in Figure 22. Further, the amino acid sequence of the framework regions of HF 21/28 antibody are described in Figure 11 and examples of humanized framework regions from HF 21/28 antibody are provided for example, in Figure 11 and various sequences provided in the sequence listing (e.g., SEQ ID NO:12, 13, 14, 15 and 107). The application also provides, for example, a nucleic acid sequence that encodes framework regions from HF 21/28 antibody. See Figure 24. Moreover, the application provides sufficient guidance regarding modifications that can be made within the framework region of HF 21/28 antibody to provide a humanized immunoglobulin light chain. For example, page 93, line 15 through page 94, line 15 provide guidance as to which amino acids within the framework regions of HF 21/28 antibody should be conserved. Applicants also describe framework regions of five different humanized light chains from HF 21/28 antibody. Thus, in view of the guidance provided in the instant application, a skilled artisan could make and use the claimed nucleic acids without undue experimentation.

The Office Action alleges that, "[e]ven minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al" (Rudikoff et al. (1982) Proc Natl Acad Sci USA 79:1979; hereafter referred to as "Rudikoff"). Although Rudikoff does disclose that a single amino acid substitution in the CDR of an antibody resulted in the loss of antigen-binding function, Rudikoff teaches that this is not typical.

> [I]t is clear that all such substitutions need not and probably do not affect antigen binding. For example, the heavy chain from the P-Cho-binding myeloma protein M167 differs from that of S107 at 13 positions (8 in hypervariable regions including a size difference) and yet has an association constant for hapten only slightly lower than S107. We have previously shown that, among anti-1,6-galactan-binding myeloma proteins, as many as eight or nine substitutions may occur in hypervariable regions with no significant effect on hapten affinity of specificity.

Rudikoff further concludes that "small numbers of substitutions in antibodies, such as those presumably introduced by somatic mutation, may in some situations be effective in altering antigen-binding specificity" (abstract, Author's emphasis). Therefore, it is clear that Rudikoff does not teach that minor changes in the variable regions of antibodies are likely to affect antigen-binding function, but rather that, except in rare instances, minor changes are likely to be tolerated.

At pages 9-10, the Office Action further alleges that,

> [i]t is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an antibody in unspecified order and fused to any human framework sequence have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims.

Applicants note that claim 13 has been amended to recite the nucleic acid encode CDR1, CDR2, and CDR3 of the non-human antibody. This amendment obviates the rejection of claims 13-15.

In view of the above remarks, Applicants respectfully submit that the specification is enabled for a nucleotide sequence encoding CDR1, CDR2, and CDR3 from a light chain of 1D9 monoclonal antibody and a framework region from the light chain of HF 21/28 antibody. Applicants request that the Examiner withdraw the rejection to claim 13 and the claims dependent therefrom.

(2) At pages 10-13 of the Office Action, claims 15, 18, and 19 were rejected as allegedly lacking enablement.

According to the Office Action, "[t]he specification is not enabling for host cells comprised within either the human patient or the transgenic animal...."

Applicants respectfully disagree with this characterization. However, in order to expedite the prosecution of this application, claims 15, 18, and 19 have herein been amended to recite "An isolated host cell." As indicated by the Office Action at page 13, lines 4-5, such amendments obviate the present rejection.

CONCLUSION

For the reasons set forth above, applicants respectfully submit that all grounds for rejection have been overcome and that all of the pending claims are now in condition for allowance, which action is requested.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to the call the undersigned at 617-521-7814.

The Petition for the Extension of Time fee is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No: 10488-218002.

Respectfully submitted,

Date: 12/18/06

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